CLAIMS

1. A multivesicular liposome having multiple non-concentric chambers with internal membranes distributed as a network throughout produced by a method comprising the steps of:

(a) forming a water-in-oil emulsion from two immiscible components, the two immiscible components being 1) a lipid component comprising at least one organic solvent, at least one amphipathic lipid, and at least one neutral lipid lacking a hydrophilic head group, and 2) a first aqueous component; said water-in-oil emulsion further comprising a non-hydrohalic acid in a concentration range from about 0.1 mM to about 0.5 M, and at least one biologically active substance, said non-hydrohalic acid and biologically active substance being independently incorporated into either the lipid component or the first aqueous component, or into both,

(b) mixing the water-in-oil emulsion containing the non-hydrohalic acid with a second aqueous component to form solvent spherules; and thereafter

(c) removing the organic solvent from the solvent spherules to form multivesicular liposomes;

wherein the non-hydrohalic acid concentration in the water-in-oil emulsion is selected to provide controlled release of the biologically active substance from the liposomes.

2. The liposome of claim 1, wherein the acid is selected from the group consisting of sulfuric acid, phosphoric acid, and acetic acid, their salts, and combinations thereof, and wherein the controlled release is at physiologic conditions.

3. The liposome of claim 1, wherein the acid is selected from the group consisting of perchloric, nitric, formic, sulfuric, phosphoric, acetic, glucuronic, citric, trichloroacetic, and trifluoroacetic acid, and salts and combinations thereof.

4. The liposome of claim 1, wherein the biologically active agent is selected from the group consisting of an antitumor agent, an anaestheic, an analgesic, an antimicrobial agent, a hormone, an antiasthmatic agent, a cardiac glycoside, an antihypertensive, a vaccine, an antiarrhythmic, an immunomodulator, a steroid, a monoclonal antibody, a neurotransmitter, a radionuclide, a radio contrast agent, a nucleic acid, a protein, a herbicide, a pesticide, and suitable combinations thereof.

5. The liposome of claim 1, wherein the biologically active substance is cytarabine.

6. The liposome of claim 1, wherein the biologically active substance is amikacin.

7. The liposome of claim 1, wherein the biologically active substance is hydromorphone.

8. The liposome of claim 1, wherein the biologically active substance is leuprolide.

9. The liposome of claim 1, wherein the biologically active substance is insulin.

10. The liposome of claim 1, wherein the biologically active substance is interleukin-2.

11. The liposome of claim 1, wherein the biologically active substance is insulin-like growth factor-1.

12. The liposome of claim 1, wherein the biologically active substance is an interferon.

13. The liposome of claim 1, wherein the biologically active substance is granulocyte colony stimulating factor (G-CSF).

14. The liposome of claim 1, wherein the biologically active substance is tumor necrosis factor.

15. The liposome of claim 1, wherein the biologically active substance is tumor growth factor alpha.

16. The liposome of claim 1, wherein the biologically active substance is tumor growth factor beta.

17. The liposome of claim 1, wherein the biologically active substance is morphine.

18. The liposome of claim 1, wherein the controlled release of the biologically active substance is sufficient to ameliorate a disease following administration of the liposome to a living mammal.

19. The liposome of claim 1, wherein the biologically active substance is selected from the group consisting of herbicides and pesticides.

20. The liposome of claim 1, wherein the amphipathic lipid is provided in admixture with cholesterol, plant sterols, or combinations thereof.

21. The liposome of claim 1, wherein the amphipathic lipid is a zwitterionic lipid.

22. The liposome of claim 1, wherein the amphipathic lipid is an anionic lipid.

23. The liposome of claim 1, wherein the amphipathic lipid is a mixture of a zwitterionic lipid and an anionic lipid.

24. The liposome of claim 1, wherein the amphipathic lipid is a mixture of a zwitterionic lipid and a cationic lipid.

25. The liposome of claims 1, 20, 22, and 23, wherein the zwitterionic lipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, sphingomyelins,

lysophosphatidylcholines, lysophosphatidylethanolamines, and combinations thereof.

26. The liposome of claims 1, 21, and 22, wherein the anionic lipid is selected from the group consisting of phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, phosphatidicacids, cardiolipins, and combinations thereof.

27. The liposome of claims 1 and 23, wherein the cationic lipid is selected from the group consisting of diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, stearylamine, and combinations thereof.

28. The liposome of claim 1, wherein the neutral lipid is selected from the group consisting of triglycerides, diglycerides, ethylene glycols, and combinations thereof.

29. The liposome of claim 1, wherein the organic solvent is selected from the group consisting of ethers, hydrocarbons, halogenated hydrocarbons, halogenated ethers, esters, and combinations thereof.

30. The liposome of claim 1, wherein the emulsification of the two immiscible components is carried out using a method selected from the group consisting of mechanical agitation, ultrasonic energy agitation, and nozzle atomization.

31. The liposome of claim 1, wherein the formation of the solvent spherules is carried out using a method selected from the group consisting of mechanical agitation, ultrasonic energy agitation, and nozzle atomization.

32. The liposome of claim 1, wherein the removal of the organic solvent is by a method selected from the group consisting of sparging, rotary evaporation, passing gas over the solvent spherule suspension, solvent selective filtration, and combinations thereof.

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33. The liposome of claim 1, wherein the concentration of the organic solvent is in the range from about 3.98 mM to about 15 mM, the concentration of the amphipathic lipid is in the range from about 3.2 mM to about 47.77 mM, and the concentration of the neutral lipid is in the range from about 0.5 mM to about 7.3 mM.

34. The liposome of claim 33, wherein the amphipathic lipid is a combination of 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) in a concentration from about 2.64 mM to about 39.44 mM and 1,2-dipalmitoyl-*sn*-glycero-3-phosphoglycerol (DPPG) in a concentration from about 0.56 to about 8.33 mM.

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